UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,031	03/16/2005	Christian Guelly	2005-0070A	1025

513 7590 07/12/2006

WENDEROTH, LIND & PONACK, L.L.P.
2033 K STREET N. W.
SUITE 800
WASHINGTON, DC 20006-1021

EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/528,031	GUELLY ET AL.	
	Examiner	Art Unit	
	Sean E. Aeder, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-65* is/are pending in the application.

4a) Of the above claim(s) *1-23,26-33 and 46-65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24,25 and 34-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *sequence comparison*.

Detailed Action

The response filed on 5/9/06 to the restriction requirement of 4/10/06 has been received. Applicant has elected Group V, drawn to a method of determining differential expression of a *polynucleotide* or diagnosis wherein a *polynucleotide* is identified, for examination. Applicant has further selected SEQ ID NO:11. It is noted that SEQ ID NO:11 represents a separate technical feature (i.e. a separate invention), and not a species. Applicant has further selected the following species: hepatocellular carcinoma (species of ailment), PCR (species of method of detecting), solid-phase screening methods (species of method of comparing), blood (species of sample from patient), and blood (species of reference sample). Because Applicant did not distinctly and specifically point out any errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Claims 1-65 are pending.

Claims 1-23, 26-33, and 46-65 are withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention.

Claims 24, 25, and 34-45 are currently under consideration.

Objections

Claims 24, 34, and 35 are objected to for reciting the unelected inventions of groups VI, VII, and unelected inventions drawn to sequences other than SEQ ID NO:11. Appropriate correction is required.

Claim 34 is objected to for reciting: "...(c) identifying said nucleic acid(s) which is (are) differentially expressed in the sample isolated from the patient compared to the reference library or the reference sample". There appear to be some words missing in claim 34. It is suspected Applicant intended the claim to recite: "...(c) identifying said nucleic acid(s) which is (are) differentially expressed in the sample isolated from the patient as compared to nucleic acid(s) in the reference library or the reference sample". Proper correction is required.

Claim 35 is objected to for reciting: "...(c) identifying said(s) nucleic acid which is (are) differentially expressed in the sample isolated from the patient compare to the reference library...". There appears to be a typographical error in claim 35. It is suspected Applicant intended the claim to recite: "...(c) identifying said~~(s)~~ nucleic acid(s) which is (are) differentially expressed in the sample isolated from the patient as compared to the reference library...". Proper correction is required.

Claim 35 is further objected to for reciting: "...matching said nucleic acid(s) identified in step (c) said nucleic acid(s) differentially expressed in a pathologic reference sample or pathologic reference library...". There appears to be a typographical error in claim 35. It is suspected Applicant intended the claim to recite: "...matching said nucleic acid(s) identified in step (c) with said nucleic acid(s) differentially expressed in a pathologic reference sample or pathologic reference library...". Proper correction is required.

Claim 36 is objected to for reciting: "...wherein step (a) at least 2 nucleic acids are identified". There appears to be a typographical error in claim 36. It is suspected Applicant intended the claim to recite: "...wherein ~~step (a)~~ at least 2 nucleic acids are identified in step (a)". Proper correction is required.

Claim 44 is objected to for reciting: "...wherein the liver disorder, is a disorder selected from the group consisting of...". There appears to be a typographical error in claim 44. It is suspected Applicant intended the claim to recite: "...wherein the liver disorder~~,~~ is a disorder selected from the group consisting of...". Proper correction is required

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24, 25, and 35-45 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 and dependent claim 25 are rejected because claim 24 omits essential steps, such omission amounting to a gap between the steps. Claim 24 recites that a polynucleotide in a sample is somehow compared with "at least one compound of a

reference library or of a reference sample" in order to diagnose hepatocellular carcinoma; however, the claims do not recite what kind of comparison would be indicative of hepatocyte carcinoma. Thus, there is a missing step involving correlating a comparison with a diagnosis. See MPEP § 2172.01.

Claim 35 and dependent claims 36-45 are rejected because claim 35 is incomplete for omitting essential steps, such omission amounting to a gap between the steps. Claim 35 recites that expression of a nucleic acid that is differentially expressed in a sample as compared to a reference library or reference sample is somehow "matched" with nucleic acids differentially expressed in a pathologic reference sample or pathologic reference library in order to diagnose hepatocellular carcinoma; however, the claims do not recite what kind of "match" would be indicative of hepatocytes carcinoma. Thus, there is a missing step involving correlating a "match" with a diagnosis. See MPEP § 2172.01.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24, 25, and 34-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application

was filed, had possession of the claimed invention. In the instant case, the claims are inclusive of a genus of fragments of SEQ ID NO:11 and a genus of variants of SEQ ID NO:11. However, the written description in this case only sets forth polynucleotides consisting of *the* polynucleotide sequence set forth in SEQ ID NO:11 and polynucleotides comprising *the* polynucleotide sequence set forth in SEQ ID NO:11. The specification does not disclose any other fragments or variants of SEQ ID NO:11, as broadly encompassed by the claims.

Independent claims 24, 34, and 35 recite methods drawn to any variant of SEQ ID NO:11. Claim 24 also recites methods drawn to a nucleic acid encoding "a polypeptide according to the sequence of...". It is noted that "a polypeptide according to the sequence of" reads on any fragment of said sequence. Thus, claim 24 reads on methods drawn to every nucleic acid sharing as few as a triplet of base pairs with a sequence (SEQ ID NO:11) encoding said polypeptide. Further, claims 34 and 35 recite: "...at least one nucleic acid according to SEQ ID...". It is noted that "a nucleic acid according to" a sequence reads on any fragment of said sequence. Thus, claim 34 reads on methods drawn to every nucleic acid sharing as few as two consecutive bases with the polynucleotide SEQ ID NO (SEQ ID NO:11) recited in claim 34 and claim 35 reads on methods drawn to every nucleic acid sharing as few as a triplet of base pairs of a nucleic acid encoding the polypeptide SEQ ID NO recited in claim 35 (the polypeptide encoded by SEQ ID NO:11). However, the written description only reasonably conveys a polynucleotide consisting of *the* polynucleotide sequences set forth in SEQ ID NO:11 and polynucleotides comprising *the* polynucleotide sequence set

forth in SEQ ID NO:11. A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common to that genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., F.3d, 2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of fragments or variants that encompass the genus of fragments of SEQ ID NO:11 or the genus of variants of SEQ ID NO:11 nor does it provide a description of structural features that are common to genera. Since the disclosure fails to describe common attributes or characteristics that identify members of the genera, and because the genera are highly variant, the disclosure of SEQ ID NO:11 is insufficient to describe the genera. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of fragments of SEQ ID NO:11 and the genus of variants of SEQ ID NO:11, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolation. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only polynucleotides consisting of *the* polynucleotide sequence set forth in SEQ ID NO:11 and polynucleotides comprising *the* polynucleotide sequence set forth in SEQ ID NO:11, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-*

Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 34 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying polynucleotides comprising *the* polynucleotide sequence set forth in SEQ ID NO:11, does not reasonably provide enablement for a method for identifying polynucleotides comprising fragments and variants of SEQ ID NO:11. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are drawn to a method for identifying polynucleotides comprising SEQ ID NO:11 or fragments and variants of SEQ ID NO:11 differentially expressed in a sample isolated from a patient relative to a reference library or reference sample. As stated above, the specification does not have a written description of fragments and variants of SEQ ID NO:11. Further, one of skill in the art would

recognize that, without a recitation of a conserved structure in the fragments and variants of the polynucleotides to which the claims are drawn, one would not be able to identify every fragment and variant of SEQ ID NO:11. Thus, it is unclear how one would perform the method as broadly claimed.

The specification teaches a method for identifying polynucleotides comprising *the* polynucleotide sequence set forth in SEQ ID NO:11 differentially expressed in a sample isolated from a patient relative to a reference library or a reference sample (Figures 3A and 3B, in particular). The specification does not provide a working example demonstrating how one would identify polynucleotides comprising every possible fragment and variant of SEQ ID NO:11 differentially expressed in a sample isolated from a patient relative to a reference library or reference sample.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to a method for identifying polynucleotides comprising fragments and variants of SEQ ID NO:11, and Applicant has not enabled said method because it has not been shown that one could predictably identify every fragment and variant of SEQ ID NO:11.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as broadly claimed.

Claims 24, 25, and 35-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for diagnosing hepatocellular carcinoma in a patient comprising comparing the expression level of a polynucleotide comprising the sequence set forth in SEQ ID NO:11 in a first blood sample from said patient with the expression level of said polynucleotide in a second corresponding blood sample from a subject known to be free of hepatocellular carcinoma and a method for diagnosing hepatocellular carcinoma in a patient comprising comparing the expression level of a polynucleotide comprising the sequence set forth in SEQ ID NO:11 in a first blood sample from said patient with the expression level of said polynucleotide in a second corresponding blood sample from a subject known to be have hepatocellular carcinoma, does not reasonably provide enablement for a method of diagnosing every liver disorder and every epithelial cancer in a patient wherein SEQ ID NO:11 or a variant or fragment thereof that is "identified" in any type of sample and "compared" in every way with just any compound of any type of reference library or of any other sample (see claim 24). Further, the specification is not enabling for a method of diagnosing every liver disorder and every epithelial cancer comprising the steps of detecting expression of every nucleic acid comprising SEQ ID NO:11 or a variant or fragment thereof in any type of sample from a patient and comparing the expression of said nucleic acid with the expression of said nucleic acid in just any reference library or any reference sample and somehow "matching" nucleic acids that are differentially expressed in the sample isolated from the patient compared to the reference library or the reference sample with nucleic acids differentially expressed in

any type of pathologic reference sample or any type of pathologic reference library wherein "matched" nucleic acids are indicative of the patient suffering from every kind of liver disorder and every kind of epithelial cancer (see claim 35). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are drawn to a method of diagnosing every liver disorder and every epithelial cancer in a patient wherein SEQ ID NO:11 or a variant or fragment thereof is "identified" in any type of sample and "compared" with just any compound of any type of reference library or of any other sample and a method of diagnosing every liver disorder and every epithelial cancer comprising the steps of detecting expression of every nucleic acid comprising SEQ ID NO:11 or a variant or fragment thereof in any type of sample from a patient and comparing the expression of said nucleic acid with the expression of said nucleic acid in just any reference library or any reference sample and somehow "matching" nucleic acids that are differentially expressed in the sample isolated from the patient compared to the reference library or the reference sample with

nucleic acids differentially expressed in any type of pathologic reference sample or any type of pathologic reference library wherein "matched" nucleic acids are indicative of the patient suffering from every kind of liver disorder and every kind of epithelial cancer.

The specification discloses a method for diagnosing hepatocellular carcinoma in a patient comprising comparing the expression level of a polynucleotide comprising the sequence set forth in SEQ ID NO:11 in a first blood sample from said patient with the expression level of said polynucleotide in a second corresponding blood sample from a subject known to be free of hepatocellular carcinoma (Example 6, in particular). The specification also discloses a method for diagnosing hepatocellular carcinoma in a patient comprising comparing the expression level of a polynucleotide comprising the sequence set forth in SEQ ID NO:11 in a first blood sample from said patient with the expression level of said polynucleotide in a second corresponding blood sample from a subject known to be have hepatocellular carcinoma (Example 6, in particular).

Horne et al (WO 02/29103 A2; 4/11/02) teaches a polynucleotide sequence, Sequence #2645, which consists of a 176 base pair polynucleotide sequence that shares 95.6% homology with 176 consecutive base pairs of instant SEQ ID NO:11 (see attached sequence comparison). Because of the high degree of homology of Sequence #2645 to a region of instant SEQ ID NO:11, one of skill in the art would recognize that reagents used to identify Sequence #2645, including polynucleotide complements of Sequence #2645, would detect polynucleotides comprising SEQ ID NO:11. Horne et al teaches a method of diagnosis of hepatocellular carcinoma wherein multiple polynucleotides, including SEQ ID NO:11 or a variant thereof, would be identified in a

blood from patient and compared with at least one compound of a reference library or a reference blood sample (page 11 lines 20-33, in particular). Said method taught by Horne et al would identify at least one nucleic acid according to SEQ ID NO:11, or a variant thereof differentially expressed in a blood sample isolated from a patient relative to a reference library or a reference blood sample comprising the following steps: (a) detecting the expression of at least one nucleic acid according to SEQ ID NO:11 or a variant thereof in a blood sample isolated from a patient, (b) comparing the expression of said nucleic acid(s) detected in step (a) with the expression of the said nucleic acid(s) in a reference library or in a reference blood sample, (c) identifying said nucleic acid(s) which is (are) differentially expressed in the blood sample isolated from the patient as compared to nucleic acids in the reference library or reference blood sample (page 11 lines 20-33, in particular). The method taught by Horne et al is a method of diagnosing hepatocellular carcinoma comprising the following steps: (a) detecting the expression of at least one nucleic acid according to SEQ ID NO:11, or variant thereof in a blood sample isolated from a patient, (b) comparing the expression of said nucleic acid(s) detected in step (a) with the expression of said nucleic acid(s) in a reference library or in a reference blood sample, (c) identifying said nucleic acid(s) which is (are) differentially expressed in the blood sample isolated from the patient as compared to the reference library or the reference blood sample, and (d) matching said nucleic acid(s) identified in step (c) with said nucleic acid(s) differentially expressed in a pathologic reference blood or sample or pathologic reference library, wherein the matched nucleic acid(s) is (are) indicative of the patient suffering from a hepatocellular carcinoma (page 11 lines 20-33,

in particular). Horne et al further teaches a method wherein detection of said nucleic acid(s) is (are) by PCR based detection or by a hybridization assay (page 13, in particular). Horne et al further teaches a method wherein the expression of said nucleic acid(s) is compared by a solid-phase based screening methods (page 19, in particular). Horne et al further teaches a method wherein the patient sample is blood (page 18 lines 25-30, in particular). Horne et al further teaches a method wherein the reference sample is isolated from a source selected from a non-diseased blood sample from another subject (page 11 lines 20-33 and page 18 lines 25-30, in particular). Horne et al further teaches a method wherein the reference library is an expression library or a data base comprising clones or data on hepatocellular carcinoma-specific expression of SEQ ID NO:11 (pages 11, 21, and 22, in particular).

The state of the prior art dictates that if a molecule such as the polynucleotide set forth in SEQ ID NO:11 or a fragment or variant thereof is to be used as a surrogate for a diseased state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis

have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Therefore, absent evidence of the polynucleotide's expression including the correlation to a diseased state, one of skill in the art would not be able to predictably use the polynucleotide in any diagnostic setting without undue experimentation.

The level of unpredictability for the detection of any disease is quite high. Since neither the specification nor the prior art provide evidence of a universal association between the claimed method of detecting the polynucleotide set forth in SEQ ID NO:11 and fragments and variants thereof and every type of ailment and using every type of sample and every type of reference, a practitioner wishing to practice the claimed

invention would be required to provide extensive experimentation to demonstrate such an association. Such experimentation would in itself be inventive.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to a method of diagnosing every type of liver disorder and every type of epithelial cancer in a patient wherein SEQ ID NO:11 or a variant or fragment thereof is "identified" in any type of sample from said patient and "compared" with just any compound of any type of reference library or of any other sample, and Applicant has not enabled said method because it has not been shown that every type of comparison of SEQ ID NO:11 or any variant of fragment thereof from any type of sample from a patient with every type of reference library or every other sample would predictably diagnose every type of liver disorder and every type of epithelial cancer. Further, one cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to a method of diagnosing every type of liver disorder and every type of epithelial cancer comprising the steps of detecting expression of any nucleic acid comprising SEQ ID NO:11 or a variant or fragment thereof in any type of sample from a patient and comparing the expression of said nucleic acid with the expression of said nucleic acid in just any reference library or any reference sample and somehow "matching" nucleic acids that are differentially expressed in the sample isolated from the patient compared to the reference library or the reference sample with nucleic acids differentially expressed in any type of pathologic reference sample or any type of pathologic reference library wherein "matched" nucleic acids are indicative of the patient suffering from every kind of liver

disorder and every kind of epithelial cancer, and Applicant has not enabled said method because it has not been shown that detecting expression of every nucleic acid comprising SEQ ID NO:11 and variant or fragment thereof in every type of sample from a patient and comparing the expression of said nucleic acid with the expression of said nucleic acid in just any reference library or any reference sample and somehow "matching" nucleic acids that are differentially expressed in the sample isolated from the patient compared to the reference library or the reference sample with nucleic acids differentially expressed in any type of pathologic reference sample or any type of pathologic reference library wherein "matched" nucleic acids are predictably indicative of the patient suffering from every kind of liver disorder and every kind of epithelial cancer.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 24, 25, and 34-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Horne et al (WO 02/29103 A2; 4/11/02).

Claims 24 and 25 are drawn to a method of diagnosis of hepatocellular carcinoma wherein SEQ ID NO:11 or a variant thereof is identified in a blood sample cell of a patient and compared with at least one compound of a reference library or a reference blood sample. Claim 34 is drawn to a method for identifying at least one nucleic acid according to SEQ ID NO:11, or a variant thereof differentially expressed in a blood sample isolated from a patient relative to a reference library or a reference blood sample comprising the following steps: (a) detecting the expression of at least one nucleic acid according to SEQ ID NO:11 or a variant thereof in a blood sample isolated from a patient, (b) comparing the expression of said nucleic acid(s) detected in step (a) with the expression of the said nucleic acid(s) in a reference library or in a reference blood sample, (c) identifying said nucleic acid(s) which is (are) differentially expressed in the blood sample isolated from the patient as compared to nucleic acids in the reference library or reference blood sample. Claim 35 is drawn to a method of diagnosing hepatocellular carcinoma comprising the following steps: (a) detecting the expression of at least one nucleic acid according to SEQ ID NO:11, or variant thereof in a blood sample isolated from a patient, (b) comparing the expression of said nucleic acid(s) detected in step (a) with the expression of said nucleic acid(s) in a reference library or in a reference blood sample, (c) identifying said nucleic acid(s) which is (are) differentially expressed in the blood sample isolated from the patient as compared to the reference library or the reference blood sample, and (d) matching said nucleic acid(s)

identified in step (c) with said nucleic acid(s) differentially expressed in a pathologic reference blood sample or pathologic reference library, wherein the matched nucleic acid(s) is (are) indicative of the patient suffering from hepatocellular carcinoma. Claim 36 is drawn to the method according to claim 35, wherein at least 2 nucleic acids are identified. Claim 37 is drawn to the method according to claim 35, wherein in step (a) the detection of said nucleic acid(s) is (are) by PCR based detection or by a hybridization assay. Claim 38 is drawn to the method according to claim 35, wherein in step (b) the expression of said nucleic acid(s) is compared by a solid-phase based screening methods. Claim 39 is drawn to the method according to claim 35, wherein the blood sample isolated from the patient is a blood sample. Claim 40 is drawn to the method according to claim 35, wherein the reference blood sample is isolated from a source selected from a non-diseased blood sample of the same patient and a non-diseased blood sample from another subject. Claim 41 is drawn to a method according to claim 35 wherein the reference sample is blood. Claim 42 is drawn to the method according to claim 35, wherein the reference library is an expression library or a data base comprising clones or data on hepatocellular carcinoma-specific expression of SEQ ID NO:11. Claim 43 is drawn to the method according to claim 35, wherein the pathologic reference blood sample is isolated from blood samples selected from a diseased sample from another patient suffering from hepatocellular carcinoma. Claim 44 is drawn to the method according to claim 35, wherein the pathologic reference library is a data base comprising data on differential expression of said nucleic acid(s) in step (a) in blood samples isolated from another patient suffering from hepatocellular

cancer relative to control expression in a reference sample or reference library. Claim 45 is drawn to the method according to claim 35, wherein the liver disorder is hepatocellular carcinoma.

Horne et al teaches a polynucleotide sequence, Sequence #2645, which consists of a 176 base pair polynucleotide sequence that shares 95.6% homology with 176 consecutive base pairs of instant SEQ ID NO:11 (see attached sequence comparison). Because of the high degree of homology of Sequence #2645 to a region of instant SEQ ID NO:11, one of skill in the art would recognize that reagents used to identify Sequence #2645, including polynucleotide complements of Sequence #2645, would detect polynucleotides comprising SEQ ID NO:11. Horne et al teaches a method of diagnosis of hepatocellular carcinoma wherein multiple polynucleotides, including SEQ ID NO:11 or a variant thereof, would be identified in a blood sample from patient and compared with at least one compound of a reference library or a reference blood sample (page 11 lines 20-33, in particular). Said method taught by Horne et al would identify at least one nucleic acid according to SEQ ID NO:11, or a variant thereof differentially expressed in a blood sample isolated from a patient relative to a reference library or a reference blood sample comprising the following steps: (a) detecting the expression of at least one nucleic acid according to SEQ ID NO:11 or a variant thereof in a blood sample isolated from a patient, (b) comparing the expression of said nucleic acid(s) detected in step (a) with the expression of the said nucleic acid(s) in a reference library or in a reference blood sample, (c) identifying said nucleic acid(s) which is (are) differentially expressed in the blood sample isolated from the patient as compared to

nucleic acids in the reference library or reference blood sample (page 11 lines 20-33, in particular). The method taught by Horne et al is a method of diagnosing hepatocellular carcinoma comprising the following steps: (a) detecting the expression of at least one nucleic acid according to SEQ ID NO:11, or variant thereof in a blood sample isolated from a patient, (b) comparing the expression of said nucleic acid(s) detected in step (a) with the expression of said nucleic acid(s) in a reference library or in a reference blood sample, (c) identifying said nucleic acid(s) which is (are) differentially expressed in the blood sample isolated from the patient as compared to the reference library or the reference blood sample, and (d) matching said nucleic acid(s) identified in step (c) with said nucleic acid(s) differentially expressed in a pathologic reference blood or sample or pathologic reference library, wherein the matched nucleic acid(s) is (are) indicative of the patient suffering from a hepatocellular carcinoma (page 11 lines 20-33, in particular). Horne et al further teaches a method wherein detection of said nucleic acid(s) is (are) by PCR based detection or by a hybridization assay (page 13, in particular). Horne et al further teaches a method wherein the expression of said nucleic acid(s) is compared by a solid-phase based screening methods (page 19, in particular). Horne et al further teaches a method wherein the patient sample is blood (page 18 lines 25-30, in particular). Horne et al further teaches a method wherein the reference sample is isolated from a source selected from a non-diseased blood sample from another subject (page 11 lines 20-33 and page 18 lines 25-30, in particular). Horne et al further teaches a method wherein the reference library is an expression library or a

data base comprising clones or data on hepatocellular carcinoma-specific expression of SEQ ID NO:11 (pages 11, 21, and 22, in particular).

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER

SEA